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09/333,703	06/16/1999	PENG CHO TANG	243/245	4404

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1637	25

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/333,703	TANG ET AL.	
	Examiner	Art Unit	
	Alexander H. Spiegler	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *1-7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Application

1. This action is in response to Paper No. 24, filed on June 25, 2003.

All arguments have been fully considered and thoroughly reviewed, but are deemed not persuasive for the reasons that follow. This action is made FINAL. Any objections and rejections not reiterated below are hereby withdrawn. Specifically, several of the 112, 2nd paragraph rejections have been withdrawn in view of Applicants' amendments and arguments, and the obviousness-type double patenting rejection has been withdrawn in view of Applicants terminal disclaimer, filed on March 10, 2003. Additionally, the 112, 1st paragraph rejections with respect to Claim 14 and the 112, 1st paragraph written description rejection with respect to Claim 15 has been withdrawn in view of Applicants' amendments and arguments.

2. Currently, claims 1-17 are pending; Claims 1-7 have been withdrawn from consideration as being drawn to a non-elected invention, Claims 8-15 were previously rejected and Claims 16-17 have been added. Claims 8-17 are rejected herein.

Priority

3. It is noted that the instant claims only have priority to June 5, 1996. Applicants claim the benefit to Application No. 08/485,323, now US Patent No. 5,880,141, which was filed on June 7, 1995, however, there is no support for the A group defined in the instant invention in the '141 patent.

THE FOLLOWING ARE NEW GROUNDS OF OBJECTION & REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS

Claim Objections

4. Claim 16 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 14. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 8-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 8-13 are indefinite because the R groups are not defined, and therefore, it is not clear as to what constitutes Formula I. Applicants should amend the claim in accordance with Formula I presented in Claims 14-17.

B) Claims 14-17 are indefinite because, for example, claims 14 and 16 are drawn to a method of inhibiting VEGF, FGF or PDGF stimulated cell proliferation in vein endothelial cells

or smooth muscle cells, however, the final step is for administering a composition comprising one or more of the compounds of Formula I. The claims do not set forth the relationship between the inhibition VEGF, FGF or PDGF stimulated cell proliferation in vein endothelial cells or smooth muscle cells and the administration of one or more of the compounds of Formula I. Therefore, it is not clear as to whether the claims are intended to be limited to a method of inhibiting VEGF, FGF or PDGF stimulated cell proliferation in vein endothelial cells or smooth muscle cells or a method of administering one or more of the compounds of Formula I.

In Claim 15, the claim does not set forth the relationship between a method of treating or preventing an abnormal condition, and the administration of a composition comprising a therapeutically effective amount of one or more compounds of Formula I.

Likewise, in Claim 17, the claim does not set forth the relationship between a method of inhibiting VEGF, FGF or PDGF stimulated cell proliferation in vein endothelial cells or smooth muscle cells, and comparing the activity of VEGF, FGF or PDGF of cells that have been contacted with one or more of the compounds of Formula I to cells that have not been contacted with one or more compounds of Formula I.

It is suggested that Applicants amend the claims to clearly set forth this relationship.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 14 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Sircar et al. (USPN 5,389,661).

It is noted that because the instant application has priority to June 5, 1996, and Sircar et al. was published on February 14, 1995, Sircar et al. is a proper 102(b).

The instant claims are drawn to a method of administering one or more of the compounds of Formula I. Sircar et al. teaches a method of administering one or more of the compounds of Formula I (see cols. 4, lines 11-42 and cols. 17-20, which teaches the base structure of instant Formula I, wherein A is an imidazole).

With respect to the recitation of "a method of inhibiting VEGF, FGF, or PDGF stimulated cell proliferation in vein endothelial cells or smooth muscle cells" this claim language is considered to be only a statement of purpose and intended result. This claim language does not result in any manipulative differences between the claimed invention and the method set forth by Sircar. The method of Sircar would appear to necessarily result in the same effect of inhibiting VEGF, FGF or PDGF since the method of Sircar includes each of the method steps of the presently claimed invention, i.e., the step of administering to a patient the chemical compound of formula I.

MAINTAINED REJECTIONS

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 12-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12-13 are indefinite over "general disease symptoms" because it is not clear what is meant by this recitation. The specification, at best, teaches *possible* disease symptoms, such as ear nodulation, tail nodulation, nose swelling, paw swelling, and ballanitis. These possible symptoms do not provide a clear definition of what is encompassed by the term "general disease symptoms".

Applicants Arguments

Applicants' argue:

> [A] person skilled in the art would know what is encompassed by the term "general disease symptoms" from the description provided in the specification and their own knowledge of the particular disease. For example, the specification describes "rheumatoid arthritis"...From this description, as well as based on one's own knowledge, a person or ordinary skill in the art would know the symptoms that a patient with rheumatoid arthritis would be present. Ear nodulation, tail nodulation, nose swelling, paw swelling and ballanitis are indicative of a specific disease state and are used for testing purposes of the same.

(see page 11 of Applicants' response of March 10, 2003)

Response to Applicants Arguments

Applicants arguments have been considered, but are not persuasive for several reasons. First, Applicants arguments with respect to "rheumatoid arthritis" are irrelevant because the claim is drawn to "general disease symptoms in said rats". Additionally, it remains unclear as to what the difference is between "general disease symptoms" versus "non-general disease symptoms". That is, the specification, nor the teachings of the art, decipher between what is considered to be "general disease symptoms" versus a "non-general disease symptom', nor does

the specification provide any teachings of how to determine "general disease symptoms". Accordingly, the rejection is maintained.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claim 15 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *treating* arthritis in a patient by administering one or more compounds of Formula I, does not reasonably provide enablement for treating or preventing endometriosis, ocular neovascularization, solid tumor growth and metastases, and excessive scarring during wound healing. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In Ex parte Forman, 230 USPQ 546 (Bd. App. 1986), the Board considered the issue of enablement in molecular biology. In considering these factors: (a) in order to practice the invention, the practitioner must test the effects of one or more compounds of Formula I in patients suffering from endometriosis, ocular neovascularization, solid tumor growth and metastases, and excessive scarring during wound healing (which are distinct conditions requiring unrelated assays); (b) the specification provides guidance for treating a patient with arthritis with compounds II-IV of Formula I; (c) working examples are presented which only teach the treatment of compounds II-IV in a rat adjuvant arthritis model; (d) the invention is directed to

methods of treating or *preventing* endometriosis, ocular neovascularization, solid tumor growth and metastases, and excessive scarring during wound healing; (e) the prior art does not teach methods of treating or preventing with one or more compounds of Formula I or that the results of an rat adjuvant arthritis model can be extrapolated to enable methods of treating or preventing endometriosis, ocular neovascularization, solid tumor growth and metastases, and excessive scarring during wound healing; (f) the level of skill in molecular biology is high; (g) the results of experiments involving treating and preventing endometriosis, ocular neovascularization, solid tumor growth and metastases, and excessive scarring during wound healing is not predictable; (h) the claims are broadly drawn, reciting the treatment and prevention of unrelated conditions, such as endometriosis, ocular neovascularization, solid tumor growth and metastases, and excessive scarring during wound healing.

Due to the large quantity of experimentation necessary to treat and prevent endometriosis, ocular neovascularization, solid tumor growth and metastases, and excessive scarring during wound healing, the lack of direction/guidance presented in the specification regarding above treatment and prevention, the absence of working examples directed to the treatment and prevention of endometriosis, ocular neovascularization, solid tumor growth and metastases, and excessive scarring during wound healing, the complex nature of the invention, the unpredictability of the treatment and prevention of endometriosis, ocular neovascularization, solid tumor growth and metastases, and excessive scarring during wound healing, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Applicants Arguments

Applicants argue that the conditions listed in Claim 15 "are blood proliferative disorders, referred to as angiogenesis and/or vasculogenesis, which result from abnormal cell proliferation", and that "because all of these disease are characterized by abnormal neovascularization and/or unregulated angiogensis" a person skilled in the art "would not endue undue experimentation in order to treat or prevent the abnormal conditions of Claim 15". (see page 14 of Applicants' response of March 10, 2003)

Response to Applicants Arguments

Applicants' arguments have been considered, but are not persuasive for several reasons. First, it is noted, contrary to Applicants' assertion, in the previous Office Action, the examiner asserted only that the specification provides enablement for a method of treating arthritis, not a method of preventing arthritis. (see page 13 of Applicants' response of March 10, 2003)

Applicants argue that because the conditions listed in Claim 15 are related, a single experiment of an adjuvant arthritis model is enabling for the treatment and prevention of endometriosis, ocular neovascularization, solid tumor growth and metastases, and excessive scarring during wound healing. This argument is not persuasive for several reasons. First, the specification has not demonstrated a direct link between the expression of VEGF, FGF, or PDGF and the above conditions. That is, these conditions can be caused by mechanisms other than angiogenesis, and specifically, other than just VEGF, FGF, or PDGF. Therefore, the inhibition of these growth does not necessarily mean that the compounds of Formula I would "treat" or "prevent" these conditions. That is, even assuming the increased presence VEGF, FGF and PDGF is a characteristic of the above conditions; the inhibition of these growth factors does not necessarily "treat or prevent" the occurrence of this conditions. Furthermore, even assuming you

could treat one of the conditions with one or more of the compounds of Formula I (for the inhibition of VEGF, FGF, or PDGF), there is no evidence that this treatment regimen or results can be extrapolated to the other conditions, especially since each of these conditions have different mechanisms and manifestations. Finally, neither the specification, nor the prior art can substantiate the use of an adjuvant arthritis model in rats as a model for the treatment or prevention of the above conditions. Accordingly, the rejection is maintained.

Conclusion

13. No Claims are allowable.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (703) 305-0806. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner are unsuccessful, the primary examiner in charge of the prosecution of this case, Carla Myers, can be reached at (703) 308-2199. If attempts to reach Carla Myers are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax number for the organization where this application or proceeding is assigned is (703) 872-9306. Applicant is also invited to contact the TC 1600 Customer Service Hotline at (703) 308-0198.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Alexander H. Spiegler
October 24, 2003

CARLA J. MYERS
PRIMARY EXAMINER